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Effect of chlorpheniramine, promethazine and cimetidine on human sperm motility in-vitro

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Sperm motility is affected by some centrally active drugs, phosphodiesterase inhibitors and drugs with local anaesthetic (or membrane stabilizing) activity (Amelar et al 1980; Hong et al 1981a). We have investigated the effects of some H_1 and H_2 antihistamines on human sperm motility.

Method

Fresh human semen samples collected from healthy volunteers who were non-smokers and non-alcoholics, and patients attending an infertility clinic were used within 2 h of collection. Only samples with a sperm count higher than 15×10^6 ml^{-1} and a transmembrane migration ratio (TMMR)—which is the % of progressive forward moving sperms—higher than 20%, were used (Hong et al 1981b). All drugs were dissolved in phosphate saline at pH 7·3 (Dulbecco A Oxoid). Sperm motility was measured using the ability of forward moving sperms to move across the 5 μm pores of a Nucleopore membrane during a 2 h incubation at 37 °C. The motility of sperms in semen buffer mixture was used as a control and those of semen-drug mixtures were expressed as percentages of the control. Aliquots of semen were mixed with buffer or drug in the ratio 2 : 1. For each of the drug dose response curves, 6 samples were tested. When histamine effects on promotheazine-induced changes in sperm motility were studied, the volumes of each of these drugs were halved so that the ratio of semen to drug mixture was kept a constant at 2 : 1.

Drugs tested in this experiment included histamine phosphate (BDH), chlorpheniramine maleate (Glaxo), promethazine hydrochloride (May & Baker) and cimetidine (SKF). The concentrations of drugs that decreased sperm motility to 50% of control (ED50) were obtained from semi-logarithmic concentration-effect curves. Statistical analysis was carried out using a paired 2-tailed *t*-test.

Results

Table 1 shows the effect of histamine and histamine antagonists on sperm motility. Neither histamine nor cimetidine in concentrations between 1 and 10 mM produced significant change in sperm motility. The two classical antihistamines, promethazine and chlorpheniramine, both produced a dose-dependent decrease in sperm motility, promethazine being the more potent. The ED50 values for promethazine and chlorpheniramine were 2·5 and 7·5 mM respectively. Table 2 shows the effect of histamine on promethazine-induced reduction of sperm mobility. Histamine antagonized promethazine-induced inhibition of sperm motility, the inhibitory effect being reduced significantly ($P < 0.01$) as the concentration of histamine was increased.

Table 1. Drug effects on the transmembrane migration ratio of human sperms (expressed as % control motility) (n = 6).

Drug concn (mM)	Histamine (mean ± s.d.)	Cimetidine (mean ± s.d.)	Prometh-azine (mean ± s.d.)	Chlorphenir-amine (mean ± s.d.)
1·0	101·0 ± 4·00	100·6 ± 3·2	*91·8 ± 2·71	94·3 ± 3·07
2·5	104·0 ± 6·07	98·4 ± 2·4	*53·2 ± 3·37	*70·0 ± 6·93
5·0	106·5 ± 7·26	98·2 ± 3·1	*38·0 ± 2·45	*58·2 ± 5·94
7·5	101·8 ± 5·31	96·0 ± 2·8	*22·2 ± 4·00	*47·8 ± 3·31
10·0	99·7 ± 4·27	89·8 ± 2·6	*15·2 ± 3·47	*39·8 ± 2·84

* Compared with histamine $P < 0.01$.

* Correspondence.

Table 2. Effect of histamine on promethazine-induced changes in transmembrane migration ratio of sperms (expressed as % of control motility) (n = 6).

Concn of promethazine (mM)	Promethazine alone (Mean ± s.d.)	Promethazine + histamine (2·5 mM) (Mean ± s.d.)	Promethazine + histamine (5·0 mM) (Mean ± s.d.)
1·0	91·8 ± 2·71	91·5 ± 2·17	97·2 ± 2·14
2·5	53·2 ± 3·37	*67·0 ± 6·78	*80·0 ± 7·62
5·0	38·0 ± 2·45	*58·0 ± 4·69	*62·3 ± 3·15
7·5	22·2 ± 4·60	*39·8 ± 3·90	*52·2 ± 3·66
10·0	15·2 ± 3·47	*24·8 ± 3·60	*38·8 ± 4·22

* Compared with promethazine alone $P < 0.01$.

Discussion

Several studies have shown that drugs with local anaesthetic properties inhibit sperm motility including procaine, propranolol (Hong et al 1981a), chlorpromazine (Hong et al 1982), and tetrahydrocannabinol (Hong et al 1981c). It is probable that the effects of chlorpheniramine and promethazine demonstrated in this study reflect their known local anaesthetic actions (Bowman & Rand 1981). The antagonism of these effects by histamine is difficult to explain, however, as histamine alone produced no significant effect, and is to be the subject of further studies. Cimetidine appears to be free of local anaesthetic properties, as it did not significantly influence sperm motility. This is consistent with its lack of local anaesthetic activity on the frog isolated sciatic nerve (Brimblecombe et al 1975).

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Potential use of an asparaginase-dextran conjugate in acute lymphoblastic leukaemia

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The relatively rapid elimination of *Erwinia carotovora* asparaginase from the circulation hampers its use in the treatment of acute lymphoblastic leukaemias. Repeated doses are required to achieve a therapeutic response and these are inconvenient to the patient. In addition, asparaginase has proved to be a potent antigen in man and repeated injections increase the risk of a hypersensitivity reaction occurring in response to the enzyme. The circulatory half-life of asparaginase has been increased by chemical modification (Blazek & Benbough (1981) and by conjugation to soluble polymers (Bendich et al 1982; Poznansky et al 1982). Benbough et al (1979) and Foster & Wileman (1979) have shown that soluble dextran-asparaginase conjugates can be prepared without extensive loss of enzyme activity, and that these conjugates have prolonged circulatory half-lives and show markedly reduced antigen reactivity (Elliott et al 1981; Wileman et al 1981). Moreover, dextran is used regularly as a plasma expander and its low toxicity is well established. This relatively simple modification procedure may have overcome the major limitations to the use of asparaginase, we have studied the circulatory properties of a dextran-asparaginase conjugate in patients with acute lymphoblastic leukaemia to assess its therapeutic potential.

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Materials

Erwinia carotovora asparaginase suitable for clinical use was purchased from British Drug Houses. Clinical dextran of 70000 daltons, dextran T fractions, Sepharose 4B and Sephadex G.25 were purchased from Pharmacia. Nesslers Reagent was prepared as described in Appendix 42 of the 1973 British Pharmacopoeia. Amino acid analysis was performed on a Chromaspek J180 amino acid analyser (Hilger Instruments, Margate, U.K.). Reagents used were of the purest grades